# TransBioLine
## Translational Safety Biomarker Pipeline

**821283 – TransBioLine**

# Translational Safety Biomarker Pipeline

# WP11 – Communication, dissemination, sustainability

# D11.4 Report on synergies with other initiatives

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# Document History

| Version | Date | Description |
|---|---|---|
| V0.0 | 10/01/2024 | First Draft |
| V1.0 | 21/01/2025 | Incorporation of partners comments |
| V2 | 27/01/2025 | Final Version |

**Acknowledgement**
This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821283. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA companies.

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# Definitions

Participants of the TransBioLine Consortium are referred to herein according to the following codes:

**UZH**. University of Zurich, Switzerland
**UMA-IBIMA**. Universidad de Málaga, Spain
**ITTM.** Information Technology for Translational Medicine, Luxembourg
**Landspitali**. Landspitali University Hospital. Iceland
**KUM**. Klinikum der Universität München. Germany
**UNOTT**. The University of Nottingham. United Kingdom
**USAL**. Universidad de Salamanca. Spain
**IR-HSCSP-ICCC**. Fundació Privada Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau. Spain
**TAM**. TAmiRNA GmbH. Austria
**SIGNATOPE**. SIGNATOPE GmbH. Germany
**ABX-CRO**. ABX-CRO Advanced Pharmaceutical Services Forschungsgesellschaft mbH. Germany
**MetaHeps**. MetaHeps GmbH. Germany
**APHP**. Assistance Publique - Hopitaux de Paris. France
**SYNAPSE**. Synapse Research Management Partners S.L. Spain
**Charité**. Charité - Universitätsmedizin Berlin. Germany
**UNEW**. University of Newcastle Upon Tyne. United Kingdom
**ULIV**. The University of Liverpool. United Kingdom
**MLM**. MLM Medical Labs GmbH. Germany
**UL**. University of Leiden. Netherlands
**SAS**. Servicio Andaluz de Salud. Spain
**PFIZER**. LTDPFIZER UK
**MSD**. Merck Sharp & Dohme Corp. USA & France
**LLY**. Eli Lilly. USA & UK
**NOVARTIS**. NOVARTIS Pharma AG. Switzerland
**ROCHE**. F. Hoffman-La Roche Ltd. Switzerland
**Janssen**. JANSSEN Pharmaceutica NV. Belgium; U.S.A.
**SARD**. SANOFI-AVENTIS RECHERCHE & DEVELOPPEMENT. France
**C-Path**. The Critical Path Institute (C-PATH) non-profit corporation. US
**UBERN**. Universitaet Bern. Switzerland

**Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the TransBioLine project (No 821283).
**Project**. The sum of all activities carried out in the framework of the Grant Agreement.
**Consortium**. The TransBioLine Consortium, comprising the above-mentioned legal entities.
**Consortium Agreement**. Agreement concluded amongst TransBioLine participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

# Abstract

Regulatory qualification of safety biomarkers for application in drug development requires robust evidence. TransBioLine was set with the aim to generate data to support this work.

In the course of the project, TransBioLine has gathered biosamples with their associated clinical data to support the development and qualification of identified candidates of biomarkers of organ injury. To achieve this goal, collaboration with other initiatives and key players have been forged, fostering not only the project but also the future envisioned framework for continued support of biomarker qualification efforts. This report provides a description of these collaborations.

This activity is part of the project Task 11.2 "Outreach and synergy with existing initiatives" within WP11 – Communication, dissemination, sustainability, which oversees the specific activities carried out by the consortium members when liaising with external stakeholders.

# 1. Introduction

Safety biomarkers help to optimize drug development and support patient safety, whereby the regulatory acceptance thereof requires substantial sample and datasets sizes to ensure adequate case and control numbers, generating robust evidence sufficient to support qualification in the selected context of use. To address this challenge, TransBioLine, a consortium of leading European research institutions, EFPIA and SMEs was established. The consortium aimed to generate exploratory and confirmatory data to support regulatory qualification of new safety biomarkers for application in drug development, establish robust datasets on DILI, DIKI, DIPI, DIVI and DINI biomarkers to enhance diagnosis of disease, work on the development of assays for new safety biomarkers and implement profiles of circulating miRNAs as tissue and mechanism specific diagnostic tools.

To support the achievement of these goals, in the course of the 72 months spanning from February 2019 to January 2025, one of the objectives of the TransBioLine consortium was to establish collaborations with synergistic initiatives and other key players in the field to enable mutual leveraging of resources and outcomes.

The aim of this document is to provide an overview of the interactions that TransBioLine has held with external stakeholders.

# 2. Methods

For the identification of synergies and collaborations, TransBioLine established a strategy for the mapping of initiatives and key players in the field of safety biomarkers identification and qualification. This strategy is described in "*D11.2 - Methodology, analysis of existing related initiatives, and tools for implementation*". This strategy consisted of identifying initiatives for collaborations that were considered relevant for the project scope and that could benefit safety biomarkers identification and qualification at large.

The process leading to the establishment of collaborations involved five essential steps that together constitute the methodological framework of reference. These five steps, Identification, Assessment, Prioritisation, Implementation and Monitoring, were previously described in D11.2.

Part of the strategy also consisted of identifying those projects and initiatives in which TransBioLine partners were already involved in, and /or where collaborations were already implicitly in place. Often these types of collaborations can be labelled as "fast-track", as collaborations can be more easily established or maintained due to common intervening stakeholders, obvious non-detrimental benefits, etc …

As also discussed in D11.2, several levels of synergies can be built according to the TransBioLine objectives, ranging from strategic alignment to outcome utilisation and joint work.

# 3. TransBioLine Synergies / Collaborations

Since the start of TransBioLine in February 2019 and based on the previously mentioned framework for synergy-mapping, consortium members have collaborated with several initiatives and key players in drug induced safety biomarkers identification and qualification.

Here below we provide a description of these collaborations and their outcome.

## Collaborations carried out with other initiatives

### DILI-sim Initiative

The drug-induced liver injury (DILI)-sim Initiative is a pre-competitive partnership between DILIsym Services, Inc. and multiple pharmaceutical companies to support the development of the DILIsym modeling software. DILIsym is a mechanistic, mathematical model of DILI in the form of computational software applied to predict whether new drug candidates will cause liver signals in patients and to enhance the understanding of mechanisms that contribute to liver safety signals already observed in the clinic. The goals of the initiative are to improve patient safety, reduce the need for animal testing, and reduce the costs and time necessary to develop new drugs.
The DILI-sim Initiative is led by Dr. Paul B. Watkins, Director of the University of North Carolina Eshelman School of Pharmacy Institute for Drug Safety Sciences. Paul B. Watkins has been engaged as Scientific Advisory Board member of TransBioLine and has provided strategic guidance and direction to TransBioLine researchers.

### eTRANSAFE Consortium

The IMI2 project eTRANSAFE (Enhancing TRANslational SAFEty Assessment through Integrative knowledge management) was initiated with the goal to develop an integrative data infrastructure with innovative computational methods and tools that aimed to improve the feasibility and reliability of translational safety assessment during the drug development process. The project, that ended in February 2023, aimed to create an infrastructure underpinned by the development of open standards and policies accepted by stakeholders, including regulatory agencies.
eTRANSAFE and TransBioLine shared six common partners, and the potential of synergies were already identified at the beginning of both projects. For this, eTRANSAFE appointed Dr Michael Merz, the former TransBioLine coordinator and advisor to TransBioLine, to become a member of the eTRANSAFE Scientific Advisory Board in 2019. Additionally, common partners between both initiatives, also facilitated the discussions and identification of synergies. Discussions held to establish the exact framework for collaboration, defined common activities within eTRANSAFE's WP7.

Initial discussions evolved around common activities within eTRANSAFE's WP7 for the validation of *in vitro* human systems.
At the project end, the eTRANSAFE Consortium organized a closing event under the title "Towards a quantum leap in drug safety assessment", where, apart from showcasing the work carried out by the Consortium, the meeting also counted with international keynote speakers. TransBioLine WP11 sustainability partners were also invited to attend their final meeting to present about TransBioLine and to take part in a panel session on sustainability. As TransBioLine was not the only IMI/IHI project invited to this meeting, valuable opportunities to exchange on project outcome sustainability were shared across several consortia with similar hurdles and goals.

**ImmUnivers Consortium**

Immuniverse is an IMI2 project formed by a European transdisciplinary consortium to understand the diversity and the biomarkers that are predictive for immune-mediated inflammatory diseases and response to therapy over the time. During 2023, WP10 members met with members of the Immuniverse project to address questions surrounding biomarker qualification processes. As a project focused on the study, management, and non-invasive monitoring using liquid biopsy and omics approaches of ulcerative colitis and atopic dermatitis, overlapping areas of research include the evaluation, development, and implementation of biomarkers in large longitudinal clinical trials allowing for expertise exchange in several area.

**LITMUS Consortium**

The IMI2 project LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis) project worked to develop, validate and qualify biomarkers for assessing NAFLD.
Dr. Daly, Dr. Anstee, and Dr. Aithal (all WP2 ) were members of both the LITMUS and TransBioLine consortiums. Synergies between the consortia applied specifically to WP2 (DILI), where biomarker data from LITMUS in regard to chronic liver diseases were useful for the selection of DILI biomarkers in TransBioLine. Even if none of the cases in LITMUS study had DILI, the overall data could be used for comparison analysis of DILI miRNA biomarkers to eliminate Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)-related biomarkers.

From this collaboration, a manuscript on miRNA biomarker sequencing in MASLD has been published, covering a large number of MASLD cases with all stages of disease well represented.

- Johnson, K. et al. Increased serum miR-193a-5p during non-alcoholic fatty liver disease progression: Diagnostic and mechanistic relevance. JHEP Reports 4, 100409 (2022).

### NeuroDeRisk Consortium

NeuroDeRisk was an IMI2 project aiming to provide novel validated integrated tools for improving the preclinical prediction of adverse effects of pharmaceuticals on the nervous system and thus help to de-risk drug candidates earlier in the R&D phases. TransBioLine team established collaborations with overlapping participation of WP5 (DINI) personnel with the nonclinical efforts of the NeuroDeRisk consortium and the ILSI/HESI Subcommittee on Translational Biomarkers of Neurotoxicity. These collaborations synergized on activities within each consortium, including sharing information on doses & routes of administration for model neurotoxicants, study designs, and related expertise, as well as combining studies results to minimize redundancies and leverage data sets to build a more comprehensive assessment of biomarker performance. WP5 also participated in a workshop on bioinformatical analysis of miRNA data held in Liverpool, UK, in February 2020.
In 2021, informal synergies continued in the case of the acrylamide study, sharing actual data and results. And in 2023, the Executive Summary of the WP5 QP was shared with the ILSI/HESI Subcommittee on Translational Biomarkers of Neurotoxicity.
From this collaboration the following manuscript has been published:

- Vlasakova, K. et al. Performance of biomarkers NF-L, NSE, Tau and GFAP in blood and cerebrospinal fluid in rat for the detection of nervous system injury. Front Neurosci 17, (2024).

### RISK.HUNt3R Consortium

RISK-HUNT3R (RISK assessment of chemicals integrating HUman centric Next generation Testing strategies promoting the 3Rs) is a European Research & Innovation project funded under the European Commission's Horizon 2020 programme. The 5-year project runs from June 2021 and builds on the outcomes of the Horizon 2020 toxicological flagship project EU-ToxRisk, ending by the end of 2021 (Home - RISK-HUNT3R).
SIGNATOPE is a partner in both consortiums and supports the project by analysing the TransBioLine candidate biomarkers in cell models and multi-organ chip systems.

The collaboration will help to understand whether the biomarkers developed in TrasnBioLine can be applied in such systems and help to replace animal toxicity testing.


**transQST Consortium**

TransQST (*Translational quantitative systems toxicology to improve the understanding of the safety of medicines*) was an IMI2 project, which started in January 2017 and ended in August 2022. TransBioLine shared 6 common partners with TransQST, which aimed to support the development of tools that should make easier to assess the safety profile of drug candidates before undergoing the clinical testing phase. Synergies between both projects were identified with TransQST's WP5 (liver) and WP6 (kidney).
Both *Strategic alignment* and *Outcome utilization* has taken place between the two projects according to the section three synergy levels. Members of TransBioLine were invited to participate in the new TransQST Model Implementation Webinar Series that kicked off in early 2021.
The interactions of the partners from the two consortia were highly enriching for the discussions held during these hands-on events on model implementation and led to strong synergies by benefitting from the data and modelling approaches generated in both projects for the development of new and safer medicines, especially in the framework of WP7 (Assay and Samples management).

## Collaborations carried out with other key players


**BBMRI-ERIC**

BBMRI-ERIC is a European research infrastructure for biobanking. This consortium brings together all the main players from the biobanking field – researchers, biobankers, industry, and patients – to boost biomedical research. To that end, they offer quality management services, support with ethical, legal and societal issues, and a number of online tools and software solutions. Ultimately, their goal is to make new treatments possible.
Mediated by Charité, the TransBioLine consortium have had access to this extensive European biobank expertise and resources. First contacts with the BBMRI-ERIC were formalised in relation to questions surrounding the assimilation of former IMI SAFE-T samples into part of TrasnBioLine. During an online meeting with members of BBMRI-ERIC, legal aspects and requirements for data and sample anonymisation were discussed.

During the General Assembly hold on September 2020, Michaela Mayrhofer as Head of Ethical, Legal and Societal Issues and Research, and Petr Holub as IT/Data Protection Manager, actively participated in the TransBioLine Sustainability webinar. The interactions with BBMRI-ERIC have been an added value for TransBioLine issuing valuable recommendations.


**BmDR**

The BmDR (C-Path's Biomarker Data Repository) advances qualification of novel biomarkers as drug development tools. The focus and major point of overlap is on kidney safety biomarkers that have the potential to significantly improve the development of new therapies by detecting kidney injury with greater sensitivity and specificity.
DIKI samples and the underlying biomarker datasets could be a foundational contribution to the developing BmDR and in return provide TransBioLine with a permanent BmDR Oversight Board position to support any TransBioLine data sustainability (continuity planning) following conclusion of the project.
Furthermore, because U.S. FDA have access to SAFE-T raw datasets and are currently reviewing PSTC novel biomarker datasets for renal tubular injury biomarkers full qualification, determining compliant options for sharing of SAFE-T / TransBioLine data to support PSTC full qualifications in USA and EU and, complementarily, sharing of PSTC data to support TransBioLine full qualifications in the EU and subsequently USA require internal TBL Governance alignment. Through these efforts, WP1 was actively contributing to the sustainability of TransBioLin and increasing the scientific/clinical knowledge around the utility of glomerular injury and renal tubular injury biomarkers to discriminate between glomerular disease only, renal tubular injury only, and simultaneous glomerular and renal tubular injury.


**Boston University School of Medicine**

A collaboration was initiated with Pr. Miklos Sahin-Toth, from the Boston University School of Medicine and WP3 (DIPI) members to understand C-terminal processing for CAPAP. Pr. Sahin-Toth reviewed and endorsed TransBioLine research plan.
Scientific exchange between Pr. Miklos Sahin-Toth and WP3 took place, and it was anticipated that a scientist from ULIV would travel to Signatope in the summer of 2021 to conduct experiments designed to identify proteoforms resulting from C-terminal proteolytic processing of CAPAP, however this work was put on hold due to COVID-19, and afterwards suspended due to other priorities in WP3.

## CIOMS DILI Working Group

The CIOMS (Council for International Organizations of Medical Sciences) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. CIOMS represents a substantial proportion of the biomedical scientific community through its member organizations, which include many of the biomedical disciplines, national academies of sciences and medical research councils. CIOMS mission is to advance public health through guidance on health research including ethics, medical product development and safety.
The CIOMS Working Group on Drug-induced liver injury issued a report on "Current status and future directions for drug development and the post-market setting". In this report the collaboration with TransBioLine was mentioned, as several members of WP2 collaborated in this effort.

## C-PATH Institute

C-Path (Critical Path Institute) is a nonprofit, public-private partnership with the Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program in 2005. C-Path joined TransBioLine Consortium as a project beneficiary without receiving funding in January 2020.
C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.
Furthermore, a collaboration agreement with C-Path's Predictive Safety Testing Consortium (PSTC) was considered at several time points during the project runtime due to the large number of overlapping partners. Discussions in 2021 with Takeda and GSK were held, as the only two EFPIA partners of PSTC at the time that were not part of TransBioLine, to review the possibility of incorporating them into TransBioLine formally. Negotiations were not successful at the time. Current still under consideration is a more limited collaboration agreement with partners of WP3 (DIPI) and WP4 (DIVI) with PSTC. The scope of the agreement is still to be defined by both sides in the coming months and is aimed at supporting the continuity and sustainability of the project workloads, but essentially it would include sharing data and expertise among both consortia, if the legal framework and the TransBioLine beneficiaries allow.
WP1 / DIKI efforts to request, analyse, and summarize data from the SAFE-T drug-induced kidney injury cohorts may support regulatory submissions that are currently being undertaken by PSTC to qualify tubular kidney injury biomarkers. By mining the clinical data collected within SAFE-T, WP1 is actively contributing to the sustainability of the SAFE-T legacy and increasing the scientific/clinical knowledge on tubular

biomarkers of kidney injury that may ultimately support those efforts being pursued within and by PSTC.
C-PATH also supported WP1 by working with them to apply for an FDA grant to be able to support WP1 ongoing qualification efforts to a greater degree moving forward having evolved as part of WP11 (sustainability) work. Likewise, discussions with C-PATH on making TransBioLine data available in their Biomarker Data Repository were held in the frame of addressing data sustainability (see collaboration with BmDR above).


**DILIN**

The DILIN (Drug-Induced Liver Injury Network) was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with the mandate of developing standardised procedures to identify and fully characterise bona fide cases of drug- and herbal dietary supplement -induced liver injury, and to conduct controlled, clinical studies that include extensive collection of data, serum, DNA and tissue specimens.
Dr. Paul B. Watkins, member of the TransBioLine Scientific Advisory Board, is also co-chair of the DILIN Executive and Steering Committees. He coordinated interactions between TransBioLine's predecessor SAFE-T and DILIN which resulted in a very important collaboration and manuscript publication regarding novel biomarkers of DILI. Close communications have continued between DILIN and TransBioline through Dr. Watkins and in 2022 Dr. Guru Aithal (WP2 lead and ExCom member as Deputy Project Coordinator) presented some of the TransBioline discoveries regarding DILI biomarkers at a Face-to-Face meeting of the DILIN. Since DILIN has serum and plasma samples obtained from over 2500 patients experiencing DILI, it is anticipated that many of the findings of TransBioLine regarding DILI may be able to be confirmed leveraging these samples.
From this collaboration the following manuscript has been published:

- Church RJ et al., Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: An international collaborative effort. Hepatology 69(2), (2019).


**NIDDK**

The Acute Kidney Injury Working Group is a public-private partnership under the auspices of FDA/NIDDK and the Critical Path Institute that provides global academic nephrology SMEs, kidney disease patient advocacy leaders, and EFPIA- and PhRMA-associated industry partners a monthly forum to identify and collectively address unmet needs in pharmaceutical drug development for acute kidney injury and for detection of drug-induced kidney injury. Multiple academic and industry participants

contribute to the NKF/Kidney Health Initiative, including PSTC, as well as TransBioLine members. The collaboration has provided:

- Annual Kidney Safety Biomarker Workshops to communicate updates for patients, nephrologists and their allied professionals, academic research leaders, regulatory agency personnel, federal and nonfederal research organizations, and industry colleagues.
- Monthly forum for informational sharing and technical interactions between biomarker leaders from the Kidney Precision Medicine Project (University of Michigan), NIDDK, NKF/Kidney Health Initiative, American Association of Kidney Patients, C-PATH BmDR, and Pharma.

**Prospective European Drug-Induced Liver Injury Network (COST Action CA17112)**

**Prospective European Drug-Induced Liver Injury Registry**

The Cooperation in Science and Technology (COST) Prospective European Drug-Induced Liver Injury Network is a Europe-wide interdisciplinary co-operative network of stakeholders in the DILI field (including scientists, clinicians, regulatory authorities, Small and Medium Enterprises (SMEs) and industry partners - 234 members from 45 countries). Raul Andrade (UMA-IBIMA) was chair, Guruprasad Aithal (UNOTT) was vice chair, and M Isabel Lucena scientific coordinator, the three of them being also members of TransBioLine. Through funding for workshops, scientific exchanges as well as training schools (Apr 2018-Apr 2023), this action coordinated the efforts aiming to advance the understanding of DILI as well as facilitated the translation of basic research and preclinical findings into clinical practice. This project was built and has developed strong links with Pro-Euro DILI Registry (led by consortium partners Universities of Nottingham and Malaga) and supported by the European Association for the Study of Liver (EASL Registry Grant 2014). This has facilitated enrolment of well-characterized patients with DILI and appropriate disease controls, with linked biological samples, as well as provide an established expert panel to adjudicate cases. PRO-EURO-DILI-NET supports global research by providing research materials and enables accessibility for training workshops to researchers from LMIC countries.
TransBioLine established close interactions with PRO-EURO-DILI-NET, as many of the recruiting sites for DILI biomarkers belonged to this Network. Throughout TransBioLine, continuous interactions between both projects have taken place to feed each other in terms of developing strategies for research development and harmonisation of patient recruitment and data collection.
In the PRO-EURO-DILI-NET meetings that took place in March 2019 and Oct 2019, Guruprasad Aithal (UNOTT) presented an overview of WP2 goals and chaired discussions on validity of current biomarkers; Jane I. Grove (UNOTT) led working groups to develop comprehensive database/ electronic registry to collate DILI patient

datasets internationally (Oct 2019, Oct 2021, Sep 2022, Mar 2023). This collaboration led to a consensus in data collection and sharing of research protocols for data and sample management and an international database of DILI patients (https://proeurodilinet.eu/), which was leveraged for the WP2 recruitment across all TransBioLine partners.

In March, 14, 2019, UMA-IBIMA SAS hosted in Malaga, the 1st "WORKING GROUP / 1st CORE GROUP and MANAGEMENT COMMITTEE MEETINGs" and the First Training School that was accredited by the Eurotox.

UNOTT hosted the COST Action "WORKING GROUPS/ 5th CORE GROUP/ 4th MANAGEMENT COMMITTEE MEETINGS / 3rd TRAINING SCHOOL" in Nottingham 11th-13th October 2021. This was attended by WP2 partners from UNOTT, UMA-IBIMA, Landspitali and LMU.

The PRO-EURO-DILI-NET wanted to secure the continuity of this network and is now the EASL DHILI Consortium, a recognised group within the European Study of the Liver (EASL) organisation. It is a multidisciplinary network of clinicians, scientists, patients, industry partners, and regulators, all with an interest in the study of Drug and Herbal & Dietary Supplement-induced Liver Injury (https://easldhiliconsortium.eu/) . The consortium hosts regular online seminars and meetings for dissemination (e.g. annually at the EASL conference). This drives forward knowledge exchange and builds a research community necessary for research into a rare condition and for funding bids.

Outputs from this collaboration have been published in the following manuscripts:

- Fernandez-Checa JC, et al. Advanced preclinical models for evaluation of drug-induced liver injury - consensus statement by the European Drug-Induced Liver Injury Network [PRO-EURO-DILI-NET]. J Hepatol. 75(4), 935-959 (2021).
- Segovia-Zafra A, et al. Preclinical models of idiosyncratic drug-induced liver injury (iDILI): Moving towards prediction. Acta Pharm Sin B. (12), 3685-3726 (2021).
- Björnsson, E. S. et al. A new framework for advancing in drug-induced liver injury research. The Prospective European DILI Registry. Liver International 43, 115–126 (2023).
- Ravindra, K. C. et al. Tandem mass tag-based quantitative proteomic profiling identifies candidate serum biomarkers of drug-induced liver injury in humans. Nat Commun 14, 1215 (2023).
- Grove, J. I. et al. Study design for development of novel safety biomarkers of drug-induced liver injury by the translational safety biomarker pipeline (TransBioLine) consortium: a study protocol for a nested case–control study. Diagn Progn Res 7, 18 (2023).
- Andrade RJ, Aithal GP et al IAIHG and EASL DHILI Consortium. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report. J Hepatol. 79(3):853-866 (2023).
- Lucena, M. I. et al. Roadmap to DILI research in Europe. A proposal from COST action ProEuroDILINet. Pharmacol Res 200, 107046 (2024).
- Segovia-Zafra A, et al. Control compounds for preclinical drug-induced liver injury assessment: Consensus-driven systematic review by the ProEuroDILI network. J Hepatol. 81(4):630-640 (2024).

## hepatoMX Project

HepatoMX EUREKA-Eurostars project application was initiated in 2024, by TAmiRNA, a TransBioLine partner, and the Dutch company You2Yourself (Y2Y), which is the legal entity responsible for organising the URMIMON study. Together, TAmiRNA and Y2Y intend to screen urine samples for microRNA biomarker signatures enabling early detection of chronic and acute liver disease. In addition, using metabolic dysfunction associated steatotic liver disease (MASLD) as an antecedent condition, it is possible to model future risk of multiple long-term conditions (such as hypertension, type 2 diabetes, chronic kidney disease, as well as cardiorespiratory fitness). This will permit stratification of those individuals at higher risk of multimorbidity and inform implementation of preventative measures at the population level. The NGS methodologies and biomarker signatures identified in TransBioLine provide a solid foundation for this project. The hepatoMX project is supported by Guru Aithal and the University of Nottingham as clinical partner contributing with sample materials. The hepatoMX project has been positively evaluated and recommended for funding by Eurostars as well as the national funding agencies in Austria and the Netherlands. The project is anticipated to begin in April 2025 and last 3 years.

## PSTC

PSTC (C-Path's Predictive Safety Testing Consortium) serves as a pre-competitive collaboration for the independent assessment, advancement, and validation of novel drug safety tests. The overlap between SAFE-T, TransBioLine and PSTC personnel on both consortia has facilitated compliant sharing of information on several topics, most notably on novel kidney injury biomarkers.

## Urimon

Urimon is a scientific study on the development of a disease warning system. The Urimon study is investigating what changes occur in the profile of miRNA in urine, as biomarkers of serious diseases with the main focus on cancer, cardiovascular and central nervous system diseases. The Urimon project combines a start-up (You2Yourself) that employs microRNA profiling for early disease detection and a non-profit biobank (Stibion) that collects periodic blood and urine samples of a cohort of 10.000 people in the Netherlands over a time span of several years. The occurrence of disease and use of medications, treatments over time, etc is monitored by 3-monthly questionnaires and coupling to GP records and national registries. They use this biobank to obtain early disease stage sample series, to validate early detection of

cancer and cardiovascular diseases. The biobank also contains many cases of people who use a variety of drugs on a regular or sporadic basis. TransBioLine shares a mutual benefit in collaboration and exchange with Urimon and invited members of Urimon to the TransBioLine General Assembly held in April 2024 in Sitges to evaluate additional avenues of extended collaboration beyond the existing collaboration of improving miRNA profiling and data interpretation methodology via TAmiRNA.

### i2b2 tranSMART Foundation

The i2b2 tranSMART Foundation is a member-driven non-profit foundation developing an open-source / open-data community around the i2b2, tranSMART and OpenBEL translational research platforms.
The i2b2 tranSMART Foundation enables effective collaborations for precision medicine through the sharing, integration, standardization and analysis of heterogenous data from healthcare providers and research institutions; through engagement and mobilization of a life sciences focused open-source, open-data community.
In TransBioLine, a project-specific tranSMART data management platform has been set up, providing an easy and robust interface for the input of new clinical and biomarker data. Several analytical tools from existing initiatives such as i2b2 tranSMART Foundation and the eTRIKS knowledge management platform have also been made available.
The TransBioLine partner ITTM, as a spin-off from the University of Luxembourg in the context of the eTRIKS IMI project, has brought in its in-depth expertise on working with the tranSMART platform. Members of ITTM have previously been active contributors to the development of tranSMART in the context of the eTRIKS consortium.
The collaboration with i2b2 tranSMART Foundation has been maintained through TransBioLine.

# 4. Conclusion

During the 6 years of the project duration, TransBioLine consortium members have been in close contact with the most relevant initiatives and key players in the field of safety biomarkers identification and qualification. These interactions and collaborations have fostered the productivity and progress of TransBioLine project objectives and supported ongoing initiatives of synergistic value in the field. As several interactions were initiated and maintained with overlapping personnel of organizations or entities without a restricted runtime, these collaborations will help to support the project legacy by ensuring that knowledge, experience, and learnings gained during TransBioLine are leveraged and applied in the work of the broader research community well beyond TransBioLine.

Previous experience shows that synergy-mapping with other projects or initiatives is more successful when both share common members, favouring a more fluent expertise exchange, stressing the importance of leveraging each partners' contacts and the concept of team-play as the basis for successful collaborations. It can be summarised that this strategy, as well as leveraging former SAFE-T personnel and legacy work, resulted in many fruitful outcomes during TransBioLine, and offers promising perspectives for the sustainability of the project legacy.